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ABSTRACT

This symposium presentation outlines the activity of the Food and Drug Administration (FDA) in regulating the use during pregnancy and lactation of drugs which affect the fetus and neonate. When presented with an unexpected adverse effect of a drug or of a class of drugs, the FDA can take several steps. These steps include ordering total removal from the market, restricting use, issuing warning statements and recommendations, providing information through official publications of the FDA, and other educational efforts. Identifying subtle adverse drug reactions is a difficult problem. Epidemiologic, prospective, retrospective, and animal studies are used. Since 1962, the FDA has required that safety studies be conducted in animals before a new drug is introduced into human subjects. Before any drug may be administered to subjects in whom there is a potential for pregnancy, teratology studies in at least two species of animals must be completed. While reproduction studies are designed to disclose teratogenic, direct toxic, gross behavioral and various other effects of the drug on the fetus or the young, they are not directed toward the detection of subtle neurological defects that may not become manifest until some time after birth. Frequently, replication of results of animal test studies is not easily obtained. (Author/RH)

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[EFFECTS OF DRUGS GIVEN DURING PREGNANCY AND LACTATION ON THE UNBORN CHILD AND NEONATE]

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The contributions of Dr. Brackbill and Dr. Butcher to an understanding of the effects of drugs on the developing organism are well known to the Food and Drug Administration which has long been concerned with the effects on the unborn child and the neonate of drugs given during pregnancy and lactation.

The Agency, appreciating the importance of detecting possible behavioral changes in infants of mothers receiving drugs during late pregnancy, has supported Dr. Butcher's experimental behavioral teratology studies since 1973.

The recent analysis by Drs. Brackbill and Broman of the effect of drugs given during labor and delivery on the subsequent behavioral development of the infant will be discussed in depth by the FDA Anesthetics and Life Support Drugs Advisory Committee on March 20, 1979. Invited attendees will also include representatives from two other advisory committees, The Fertility and Maternal Health Advisory Committee and The Psychopharmacologic Drugs Advisory Committee. Thus anesthesiologists, obstetricians, neonatologists, pediatricians, and statisticians will contribute to the discussion and their recommendations can be expected to carry great weigh with the Agency.

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There are a number of steps that the Agency can take or has taken when presented with an unexpected adverse effect of a drug or of a class of drugs. If circumstances are compelling, a drug may be removed entirely from the market, or certain restrictions may be placed on its use. Thus a proposal has been published in the Federal Register to withdraw approval of the New Drug Applications for Sparteine Sulfate Intramuscular Injection and Oxytocin Citrate Buccal Tablets on the grounds that these drugs are not found to be safe for use in the induction of labor and treatment of hypotonic uterine contractures. As with all oxytocics, both may cause uterine tetany and fetal distress. Because of the manner of administration of the intramuscular and oral preparations, strict control of their effects is not possible. Oxytocin given by intravenous infusion at a controllable rate is much safer. New labeling restrictions have been placed on injectable oxytocin itself, eliminating its use for elective induction of labor and restricting the route of administration for medical induction of labor to intravenous drip only. Elective induction of labor with oxytocin poses risks for women and fetuses that are unacceptable when the only benefits are convenience to doctors and patients and intravenous drip which provides the most accurate control of dosage is the only acceptable method of administration when medical induction of labor is indicated.

If possible risks to the fetus or infant do not clearly outweigh possible benefits to either mother or child, a warning statement may be placed in the package insert, the official labeling of the drug. Thus, the labeling of minor tranquillizers calls attention to an apparent increased risk of congenital malformations associated with the use of these drugs during the first trimester of pregnancy. It also points out that because the use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided and recommends that patients be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirablity of discontinuing the drug.

Even when the benefits of the drug to the mother may out weigh the risks to the fetus, as for example, the use of diphenylhydantoin in epilepsy, information on known or suspected birth defects is placed in the labeling. Such information is in the labeling for diphenylhydantoin and other anticonvulsant drugs. Physicians may be promptly alerted to such labeling changes through the FDA Drug Bulletin, an official publication of the Agency issued periodically and sent to physicians, pharmacists and certain other health professionals.

FDA's educational efforts have also been directed towards the patient through the medium of patient package inserts that must be provided to the patient by the pharmacist or physician when the drug is dispensed. The inserts are designed to provide information about safety of and effectiveness of the drug and to assist the patient in complying with the physicians instructions or to help her reach a decision of whether or not she wishes to take it. To date, such inserts have been limited to oral contraceptives, progestins and estrogens. These inserts contain warnings of the apparent increased incidence of malformations in infants whose mothers have taken these drugs during early pregnancy, or in the months immediately preceding pregnancy; they describe the risk of vaginal adenocarcinoma and genito-urinary defects in female and male offspring exposed to estrogen during pregnancy. Expanded use of patient package inserts awaits the results of ongoing studies with regard to such questions as to which drugs should require patient package inserts, the type of information that should be contained in these inserts to make them truly effective, and the best method of insuring that these inserts reach the patient.

The detection of subtle adverse drug reactions, particularly if they occur in only a small percent of exposed individuals or are not manifested until some time after exposure, is a

serious problem. Epidemiologic studies are usually necessary both to establish a cause and effect relationship of the association and to give some idea of the magnitude of the risk. Large scale prospective studies such as the Collaborative Perinatal Study that furnished the data discussed by Dr. Brackbill are unfortunately rare. Recourse often must be had to retrospective studies and indeed the Food and Drug Administration is funding one such study designed to compare the physical and behavioral development of 1600 offspring exposed in utero to ultra sound and 1600 non-exposed controls. Both prospective and retrospective studies are complicated by compounding factors such as socio-economic and genetic backgrounds, concomitant exposure to other drugs or other environmental chemicals; intercurrent infections or illnesses etc. Epidemiological studies are also difficult in the absence of a large scale record linkage system such as is common in countries that have a national health insurance scheme. However a number of privately funded systems in the U.S. as the Kaiser Foundation health plan system and the Mayo Clinic Registry have provided epidemiologic data to the Food and Drug Administration with regard to drug intake and birth defects. Other sources include birth defects monitoring programs such as those maintained by the Center for Disease Control of the United States Public Health Service in

Atlanta, Georgia and by the New York State Department of Health in upstate New York. Information with regard to the mothers exposure to drugs during pregnancy must obtain retrospectively through the attending physician.

This brings us to the question as to the value of animal experiments, either to alert to possible adverse effects in human subjects or to establish whether or not an observed adverse effect is indeed drug related. When associations between drugs and birth defects in man are reported, more extensive studies in animals, particularly in subhuman primates, may help establish a causal relationship. A notable example is the 1964 report of phocomelia in baby monkeys whose mother received thalidomide in early pregnancy in a dosage approximating the human dose, whereas studies in rats, rabbits and mice using huge doses gave equivocal information. More recently, diethylstilbestrol administered to pregnant monkeys was found to cause birth defects in the offspring similar to those reported in human beings, including cervical hooding and vaginal adenosis in females and external genitalia abnormalities in the male.

Since 1962, the Food and Drug Administration has required that appropriate safety studies be conducted in animals before a new drug is introduced for the first time into investigational drug subjects. The type of tests required

vary to some degree with the type of drug and the proposed clinical trials Guidelines are available to assist the sponsor in selection of the appropriate tests.

The current guidelines include a three segment reproduction study. One is a traditional reproduction study in which both males and females receive the drug before mating and administration to the mother is continued throughout pregnancy, parturition and nursing. The second segment consists of the administration of the drug to the mother during the period of organogenesis and is designed to detect teratogenetic effects. The third segment, the prenatal and postnatal study consists of administering the drug in the last third of pregnancy and up to the time of weaning.

As a general rule, before any investigational drug may be administered to subjects in whom there is a potential for pregnancy, teratology studies in at least two species of animals must be completed. The results of these tests and of any experience in human pregnancies must be revealed to clinicians undertaking investigational studies and in the labeling of marketed drugs.

Reproduction studies are in general designed to disclose teratogenic effects as well as effects on fertility, gestation, parturition, lactation, and maternal care and the

direct toxic effect and gross behavioral effects of the drug on the fetus or the young. They are not expressly directed towards the detection of subtle neurological defects that may not become manifest until sometime after birth.

Numerous studies in both human subjects and animals establish without doubt that such effects may be associated with drug use (and parenthetically, both beneficial and detrimental effects have been reported). The present state of the art in the field of behavioral teratology testing is such that is difficult to require studies absence assurance that they would yield meaningful data. The Food and Drug Administration through the National Center for Toxicological Research hopes to further develop the methodology and to this end has enlisted the support of several experts in the field. NCTR is a bureau of the FDA that is devoted entirely to toxicological research and development. EPA supplies some financial support for the Center's research operations which include studies concerned with carcinogenicity, mutagenicity, and teratology.

Finally, it should be recognized that screening tests in animals while serving an important function, have many obvious shortcomings. Even if small animals are used, the expense is such that only a limited number of animals can be used and therefore recourse must had to administration

dosages greatly in excess of the human dose on a milligram/kilogram basis. Species and strain differences in response to drugs are well known. Every attempt must be made to select an animal model that not only metabolizes a drug in a similar fashion as man so that safety of both the drug and its metabolites may be established but also one whose structural and functional development approximates that of man.

One final point, experience has shown that a procedure that appears to yield fruitful results in the hands of one investigator may fail to yield comparable information in the hands of another. More importantly, that a procedure that yields meaningful and reproducible results in the hands of one or more skilled investigators working in a cloistered atmosphere may prove totally unreliable when conducted on a routine basis by unskilled and/or poorly supervised technicians. The call for more preclinical studies both for drugs and other environmental chemicals such as pesticides and food additives has placed heavy demands on testing laboratories. After a number of examples of poorly or fraudulently conducted preclinical (animals) studies including reproduction studies had been uncovered by the Food and Drug Administration, an agency wide Bioresearch Monitoring Program was initiated two years ago, under which biennual inspections will be undertaken of all laboratories conducting such studies.